REMARKS

Claims 1-114 were pending in the present application. Claims 11-17 and 42-114 were withdrawn from consideration. By virtue of this response, claims 1, 4, 5, 7, 18-27, 30, 31, 33- 41 have been amended. Accordingly, claims 1-10 and 18-41 are currently under consideration. Amendment of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. Support for the amendment of the amended claims can be found throughout the specification, including the claims as originally filed, and particularly at page 7, lines 30-23; page 8, lines 4-9 and lines 25-28; page 16, lines 5-16; page 18, lines 9-19; page 23, line 22 through page 24, line 8; and Example 1. The amendment of the specification corrects usage of trademarked terms and updates the supplier. No new matter is believed to have been added.

With respect to all amendments and canceled claims, the Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. The Applicant expressly reserves the right to pursue any unclaimed subject matter in one or more continuation or divisional applications. The Applicant notes that the Examiner recognized in the Restriction Requirement (mailed 6/8/2004) that groups I and II are linked by claim 1. The Examiner additionally stated that upon indication of allowable subject matter of the claim 1, the restriction requirement as to groups I and II shall be withdrawn and any claims depending from or otherwise including all the limitations of the allowable linking claims will be entitled to examination in the present application. The Applicant further notes that upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species and subspecies as provided by 37 CFR 1.141.

Regarding the Information Disclosure Statements

The Applicant thanks the Examiner for review of the references and return of the initialed PTO-1449 forms. However, the Applicant notes that the Examiner did not initial reference no. 78 (IDS filed May 9, 2002) (Weiss *et al.*, (1987) *Bull. Hosp. Jt. Dis. Orthop. Inst.* **47**:31-39.) The Applicant respectfully requests clarification of why this reference was not initialed and note

that this reference differs from Weiss *et al.,* 1986 (reference 77). Should the Examiner require a duplicate copy of the reference for review, the Applicant is happy to provide one upon request.

The Applicant notes that a Supplemental Information Disclosure Statement is filed herewith. The Applicant respectfully requests review of the submitted references and return of the initialed PTO-1449. Should any of the references be missing from the Supplemental Information Disclosure Statement the Applicant is happy to provide additional copies upon request.

Regarding the Objection to the Abstract

The Abstract has been amended (see "Amendments to the Abstract"). The Applicant thus respectfully requests withdrawal of the objection.

Regarding the Objection to the use of Trademarks

The specification has been amended in view of the Examiner's objection. The Applicant notes that the specification at page 19 clearly states the composition of ZYDERM, as well as the supplier. The generic composition is evidenced by the product insert submitted in the Supplemental Information Disclosure Statement co-filed herewith. Similarly, the specification has been amended for the use of the trademark CHIROCAINE (levobupivacaine for injection), and the product information insert is submitted in the Supplemental Information Disclosure Statement submitted herewith.

Should the Examiner require further documentation or amendment, the Applicant respectfully requests clarification of such requirements.

Rejections under 35 U.S.C §112

Claims 7, 18-26, 30, 31, and 33-41 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention. The Applicant respectfully traverses the rejection.

While not acquiescing to the Examiner's statements regarding the above-listed rejection, in order to efficiently move forward the prosecution of the present application, the Applicant has amended claims 7, 18-26, 30, 31, and 33-41 to even more clearly point out and distinctly claim the subject matter the applicant regards as the invention. Applicants thus respectfully request withdrawal of the rejection of claims 7, 18-26, 30, 31, and 33-41 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §102(b)

Claims 1-3, 8-10, and 26 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Pavelka et al., Poster No. 137 of "Safety Following Intra-articular Injection of NeuVisc™ --Two Studies" Fourth World Congress of the Oslo Arthritis Research Society International, Vienna, Austria, total pages 2, September 1999. The Applicants respectfully traverse this rejection.

While not acquiescing to the Examiner's statements regarding the above-listed rejection of claims 1-3, 8-10, and 26 over Pavelka et al., in the interests of efficiently moving the prosecution forward the Applicant provides the following comments.

The Applicant asserts that Pavelka et al., does not teach every limitation of independent claim 1 and therefore its dependent claims 2-3, 8-10 and 26. As noted in the present specification and explained further below,[1] the NeuVisc™/0.3% lidocaine composition described in Pavelka *et al.,* would not release *an effective amount* of the pharmaceutical agent from the collagen *for at least 48 hours*.

The material Pavelka used in his clinical trials was NeuVisc™, which is 65 mg/mL collagen, with 0.3% lidocaine (3 mg lidocaine per mL) added. Pavelka administered 1.0 mL of this formulation in his first study, and 2.0 mL in his second study, resulting in a lidocaine dose of either

[1] The Applicant notes for the Examiner's convenience that each of the references cited in these remarks are included in the Supplemental Information Disclosure Statement filed herewith.

3 or 6 mg. As explained below, there is literature that demonstrates that, at these low doses, lidocaine has no clinical relevance for therapeutically effective sustained relief of pain.

Local analgesics (*e.g.*, lidocaine, bupivacaine, etc.) are routinely administered into the knee joint after arthroscopy, typically as a bolus. Generally a dose of 50-150 mg of bupivacaine is used (Meinig RP, *et al.*, "*Plasma bupivacaine levels following single dose intraarticular instillation for arthroscopy*" *Am J Sports Med* (1988) **16**:295-300; Liguori GA, *et al. "Possible bupivacaine toxicity after intraarticular injection for postarthroscopic analgesia of the knee: implications of the surgical procedure" Anesth Analg* (2002) **94**:1010-3; and Henderson *et al., "Postarthroscopy analgesia with bupivacaine. A prospective, randomized, blinded evaluation*" *Am. J. Sports Med.* (1990) 18:614-617). In particular, Henderson *et al., ibid* note that bupivacaine delivered intraarticularly at the conclusion of arthroscopic surgery to the knee joint actually appears to be rapidly cleared from the joint and appears to offer little or no reduction in pain after within 1 to 2 hours after injection. It is known that bupivacaine has a duration of action (or half-life) of 3.5 hours which is 2 to 3 times longer than lidocaine (Spivey WH, *et al,. "A clinical comparison of lidocaine and bupivacaine" Ann Emerg Med.* (1987) **16**:752-757; *Physicians Desk Reference*, Medical Economic Company, Montvale NJ, 53rd edition). Further, the Physician's Desk Reference (PDR) reports that the potency of bupivacaine is also greater than that for lidocaine. Namely, 2 to 10 times more lidocaine is required to achieve the same clinical efficacy as provided by bupivacaine for equivalent indications. Therefore, Pavelka administered no more than 3% of the lidocaine dose considered clinically effective for reducing pain and thus the formulations reported by Pavelka could not have contained a therapeutically effective amount of lidocaine for the treatment of pain or discomfort either at the time of administration or after 48 hours or more.

Further experimental support for the comments above can be found in Creamer *et al.* ("*Pain mechanisms in osteoarthritis of the knee: effect of intraarticular anesthetic*" *J Rheumatol.* (1996) **23**:1031-1036), which reports statistically significant decrease in pain scores at 1 hour post-intra-articular administration of 12.5 mg bupivacaine in the knees of osteoarthritis patients. In other words, achieving an analgesic effect for just 60 minutes would require a lidocaine dose of at least 25 mg, which is a more than four times the dose that Pavelka used.

Additionally, as would be apparent to scientists in the field, the results Pavelka describes, in which 81% of the subjects receiving collagen with 3 mg of lidocaine reported decreased pain, were describing patient pain levels at 6 weeks after injection. As noted above, there is no way that the analgesic/anesthetic effects of the amount of lidocaine administered could possibly be responsible for the diminished pain experienced by patients at this time and thus Pavelka is not describing a formulation for delayed release of an amount of lidocaine effective in lessening pain.

Pavelka also notes that improvement (lessening of pain) was gradual and tended to increase through the final 6-week visit. The gradual lessening of pain suggests to those of skill that it is the collagen suspension itself, which is intended as a viscosupplement for joint synovial fluid, that is responsible for the reduction in pain and is consistent with Pavelka's statement that "the current formulation does not contain lidocaine" (Pavelka *et al.*, (September 1999) *Fourth World Congress of the OsteoArthritis Research Society International*, Vienna, Austria), and clearly indicates his belief that the lidocaine was not the "active" agent in this therapy. As noted by Pavelka (Pavelka *et al.*, (June 1999) Poster No. 001096 XIV *European League Against Rheumatism Congress*, Glasgow, Scotland and (June 1999) *4th Congress of the European Federation of National Associations of Orthapaedics and Traumatology*, Brussels, Belgium), "viscosupplements are believed to provide shock absorption protection to joint tissues. . . ."

Thus, for the reasons described above, the data reported in the literature support the conclusion that a total dose of 3 to 6 mg of lidocaine provided by the 1 or 2 mL intra-articular injections cannot be clinically relevant at 6 weeks and that the formulations of Pavelka do not provide any sustained release of therapeutic amounts of lidocaine.

Further, the ratio of collagen:pharmaceutical agent recited in claim 1, as amended, and thus its dependent claims is not taught in the reference, as noted by the Examiner at page 7 of the Office Action (dated October 12, 2004). Thus, every limitation of the claims is not taught by the reference (the composition of Pavelka and the claimed compositions are different) and the

functional limitations, as evidenced by the teaching of the present specification, are not inherent in the composition disclosed by the reference.

In view of the above remarks, the Applicant respectfully requests that the rejection of claims 1-3, 8-10, and 26 under 35 U.S.C. 102(b) be withdrawn.

Rejections under U.S.C. §103(a)

While the Applicants do not agree with the basic assertions put forth by the Examiner with respect to the rejections under 35 U.S.C. §103, in the interests of efficiently moving the prosecution of the present application forward, Applicants provide the comments appearing below.

Claims 1-10 and 18-41 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Pavelka et al., Poster No. 137 of "*Safety Following Intra-articular Injection of Neu Visc™--Two Studies*" *Fourth World Congress of the Oslo Arthritis Research Society International*, Vienna, Austria, total pages 2, September 1999 with Yamahira *et al.* (U.S. Patent No. 4,855,134), Maeda *et al.* (*Journal of Controlled Release*, Vol. 62, pp. 313-324, 1999), Batyrov *et al.* (*Stomatologiya*, Vol. 61, No. 2, pp. 7-10, March-April, 1982, English Abstract Only) and Solanki *et al.* (*Arthroscopy*, Vol. 8, No. 1, pp. 44-47, 1992). The Applicants respectfully traverse this rejection.

As noted above, the Applicant has reviewed the above-cited reference Pavelka *et al.*, and respectfully notes that the composition described by Pavelka does not meet the limitations of claim 1, and therefore its dependent claims. Further, the Applicant asserts that the combination of the cited secondary references does not render independent claims 1 and 27, and therefore their dependent claims, obvious.

A *prima facie* case for obviousness requires, *inter alia*: (1) a suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the cited reference; (2) a reasonable expectation of success; and (3) that the reference

teach or suggest all of the elements of the claimed invention. MPEP §2143. None of these requirements are satisfied by the cited references

As noted above, Pavelka et al. provides no teaching or suggestion that the disclosed composition can be formulated to release an effective amount of the pharmaceutical agent from the collagen for at least 48 hours or that the compositions be formulated with collagen and pharmaceutical agent in a ratio of from about 0.5:1 to about 10:1 collagen:pharmaceutical agent. As noted above, given the 3 mg or 6 mg dose of lidocaine administered by Pavelka the pain relief experienced by the patients at 6 weeks cannot be related to the amount of lidocaine, as an effective dose was not present, even 1 hour after initial injection, let alone at 6 weeks post-injection. As noted by Pavelka, NeuVisc™ is a synovial fluid supplement. "Viscosupplements are believed to provide shock absorption protection to join tissues after intra-articular injection." (*See* Pavelka et al. page 1, col. 1.) Thus the pain relief of Pavelka, as would be understood by one of skill in the art, is related to the shock absorption provided by being a viscosupplement and is not related to the amount (0.3%; 3 or 6 mg) of lidocaine, which is an amount not therapeutically effective, as noted in the present specification. (*See* page 20, lines 1-10.)

None of the secondary references supply the teaching or suggestion that the collagen recited in the claims would be able to modify the release rate of the pharmaceutical agent to provide sustained release at therapeutically effective levels for at least 48 hours. Additionally, as described in greater detail below, persons of skill in the art would not expect the collagen recited in the claims to be able to modulate the release of the active ingredients as specified in the claims, thus, from the point of view of the skilled person, there is little likelihood of success for achieving sustained release of the pharmaceutical agent using the collagen formulation recited in the claims.

As known to those of skill in the art of collagen formulations, particularly in the use of collagen formulations for drug delivery, the form of collagen used is important to the characteristics of drug release from the collagen. Additionally, it is also known that the different forms of collagen have very different physical characteristics and are not expected to have the same physical properties, *i.e.,* they are not expected to have the same effect on release rates for drugs or other

compounds. Thus, generally, fibrillar and non-fibrillar collagen are not equivalent and neither are non-crosslinked and cross-linked collagen, or soluble and insoluble collagen, just for example. (*See e.g.,* Wallace *et al., Advanced Drug Delivery Reviews* (2003) **55**: 1631-1649) Further, a given type of collagen can be "formulated" in different ways that would also affect the properties of drug release. For example, collagen in a film, matrix or membrane will have different physical properties and different drug release rates than solutions of soluble collagen, which will again differ from suspensions (or gels) of insoluble collagen. Scientists working in the field of controlled release of therapeutically active ingredients and collagen formulations also understand that the release properties for a given formulation are not only dependent upon the "carrier" or "inactive," but also upon the characteristics of the active (drug) itself. For example, is the active a macromolecule, such as a protein, or a small molecule?

Prior to the priority date of the present application, it was generally thought in the field that in order to observe moderated release rates for drugs/active ingredients from fibrillar collagen the formulation must be treated in some manner to chemically bind the active and the collagen or the active must be large enough for its diffusion from the collagen matrix to be hindered. For example, Rosenblatt *et al.,* (*J. Controlled Release* (1989) **9**: 195-203) state that "Fibrillar collagen matrices were capable of moderating the release rates of very large proteins *only* (such as fibrinogen) and a *significant non-fibrillar content was necessary* to modulate the diffusivity of smaller proteins such as chymotrypsinogen" (Abstract, emphasis added) and "In order to control the release of small proteins by hindering the diffusion rates, the matrix must contain a significant concentration of non-fibrillar or microfibrillar collagen " (pg. 203 "Conclusions"). Typical anesthetics and/or analgesics are far smaller than even the small proteins discussed by Rosenblatt et al., (for example, bupivacaine has a molecular weight of 325 (http://ramanathans.com/localchapterram[1].htm)), and there would be no expectation by those of skill in the art that the modulated release of the proteins described by Rosenblatt would be observed for small molecules of this size. Thus, as Rosenblatt *et al.,* demonstrates, those in the field, would not expect that formulations containing an aqueous dispersion of insoluble non-crosslinked type I fibrillar atelopeptide collagen (the collagen as recited in the claims) and an anesthetic or analgesic

would result in sustained release at a therapeutically effective level of the anesthetic or analgesic for at least 48 hours. However, example 1 of the present specification clearly demonstrates that sustained release is achieved in the exemplified formulation of collagen/bupivacaine and that this sustained release was at a dose that would be effective in lessening joint pain due to arthroscopy.

Even after the filing date of the present application the accepted view by those of skill was that small molecules would not experience hindered diffusion (modulated release rates) from fibrillar collagen suspensions, as noted by Wallace[2] et al., in a review of the field of collagen suspensions in 2003. *See e.g.,* Wallace, *ibid*, Section 3.2, pg. 1638, col. 2: "Release of small molecules": "Based on the reasoning about collagen structure, drug molecules (mol. wt. 0.5 to 2 kDa, molecular dimensions 9.5 to 1.5 nm) should not experience hindered diffusion in transport through FCS (mesh size estimate: 58 nm). . ." (where "FCS" is fibrillar collagen suspension) and "Diffusion-dominated release of dissolved small molecules from collagen gels may be predicted to resemble that in Fig. 3 … [ref 38]. The drug was 80% depleted in only about 8 min." To overcome this rapid diffusion-controlled release for small molecules, scientists in the field would expect it to be necessary to somehow bind the drug to the collagen, otherwise treat the formulation to hinder the release rate (*e.g.,* cross-linking), or require additional components such as non-fibrillar collagen. They would not expect that an "untreated" aqueous dispersion of insoluble *non-crosslinked* type I *fibrillar* atelopeptide collagen, as recited in the claims, would modulate the release rate of the active as shown in the present application.

Certain of the secondary references cited by the Examiner in fact also appear to teach away from modification of the composition of Pavelka as a controlled release formulation and to support the characterization of the knowledge of the skilled practitioner as described above, namely, that fibrillar collagen dispersions would only modulate release of actives such as macromolecules (*e.g.,* very large proteins), *unless* the collagen was somehow bound to the active or otherwise treated to retard the rate of release of the active. The references, particularly Yamahira *et al.*, and Maeda *et*

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[2] Don Wallace, the lead author, is an expert in the field of collagen formulations and was for many years a scientist at Collagen Corp. and Cohesion Inc., as well as being an inventor on numerous of the patents issued to these companies.

al., also support the remarks presented above, pointing out that not all collagen formulations are equivalent and that the type of collagen and how the collagen is prepared can influence whether and/or how much the formulation will modulate release of an active. The cited references are discussed in greater detail below.

Both Yamahira *et al.*, and Maeda *et al.*, teach that to form controlled release collagen formulations, the collagen and drug must be prepared as a dry solid (*e.g.,* a non-liquid matrix) to achieve the sustained release properties. Yamahira *et al.,* teach that collagen that is mixed with indomethacin or interferon (a protein) and then dried to a solid will form a sustained-release preparation that can be used either as a solid implant (*see e.g.,* col. 4, 35-65) or as a powdered solid which can then be suspended in a viscous fluid such as vegetable oils, polyethylene glycols, propylene glycol, etc. for injection (*see* col. 4, lines 5-23; Examples 5-7). There is no suggestion that the composition be formulated as a dispersion in an aqueous liquid and, in fact Yamahira *et al.,* suggest that the inclusion of substances other than the carrier and active ingredient can promote the more rapid release of active ingredient and are not preferred (col. 3, lines 57-63). Maeda *et al.*, teach that the manufacturing technique and ultimate solid physical form of the collagen/active formulation are critical to the controlled release properties of the formulation. ("The results of the release experiments indicate that HAS release from the minipellet is mainly controlled by diffusion in the collagen matrix, and that sustained release is achieved by the dense structure of the collagen matrix *which is formed in the manufacture process.*" Abstract, emphasis added.) These conclusions are supported by the comparison in Maeda *et al.,* of three forms of the collagen/drug formulation, namely the "collagen film," "collagen sponge," and "collagen minipellet." As noted by the authors, for example, the release rate from the collagen sponge was "extremely rapid" (see page 316, col. 2, 3rd full paragraph). Study of the minipellet, which is formed by an extrusion/molding process, led Maeda *et al.,* to conclude that "the minipellet has unique directional release behavior caused by its microstructure" (*see* Abstract).

Thus, these references support the statements in example 1 (pages 26-27, bridging paragraph) of the present specification and the remarks above that the sustained release characteristics of the claimed compositions are unexpected because the collagen recited in the

claims (an aqueous dispersion of insoluble non-crosslinked type I fibrillar atelopeptide collagen) has not previously been used to control the release of pharmaceutical agent and those of skill in the art, especially in view of the cited references Yamahira *et al.* and Maeda *et al.,* but also in view of the references commented on above (Wallace *et al.,* and Rosenblatt *et al.*), would expect certain treatment (*e.g.,* cross-linking) or manufacturing methods (*e.g.,* drying and/or extrusion of a solid) to be necessary to provide a collagen sustained release formulation. Relatedly, one of skill in the art, in view of these references, would have no expectation that the claimed formulations would have the claimed sustained release properties and no motivation to modify Pavelka to achieve these properties. Batyrov et al., (abstract only, which refers only generically to "collagen") and Solanki *et al.,* do not appear to provide any motivation to overcome the teachings of Maeda *et al.* and Yamahira *et al.* Therefore, the Applicant respectfully asserts that the combination of these references does not render the claimed compositions and methods obvious.

In view of the above remarks and amendment of claim 1 the Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-10 and 18-41 under 35 U.S.C. §103(a).

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is earnestly invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **437252001200**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 17, 2005

Respectfully submitted,

By _____

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